or cDNA insert, and (3) upon hybridization of said cohesive circularization ends, said cohesive circularization ends cannot be [are not] substantially covalently joined by ligase.

Please add Claims 67 and 68.

--67. A method for insertion of a nucleic acid fragment into a circular vector, wherein said method is substantially equally efficient when the amount of said nucleic acid fragment ranges from 10^{-21} to 10^{-14} moles.

68. A method for insertion of a nucleic acid fragment into a linear vector, wherein said method is substantially equally efficient when the amount of said nucleic acid fragment ranges from 10^{-21} to 10^{-14} moles.--

REMARKS

Applicant thanks Primary Examiner Brusca for his helpful commentary and suggestions during the telephone interview. Favorable consideration of all the pending claims is respectfully requested.

Applicant notes that the Examiner has not provided his initials next to the Upcroft et al., *Rapid and efficient method for cloning of blunt-ended DNA fragments*, GENE 1987; 51(1): 69-75 reference listed in the Information Disclosure Statement provided by the Examiner with the Official Action. Applicant respectfully requests that this reference be considered and that the Examiner forward a copy of the Information Disclosure Statement which has his initials next to this reference.

Sequence Listing:

As requested by the Examiner, Applicant has amended the specification to correct

inadvertant errors of deletion in the listing of sequences in the Sequence List.

Pursuant to 37 C.F.R. § 1.821(g), or alternatively 37 C.F.R. § 1.825(a), the undersigned states that the Substitute Sequence Listing submitted herewith is fully supported in the application as filed and contains no new matter.

Applicant submits herewith a copy of the Substitute Sequence Listing in computer readable form in compliance with 37 C.F.R. § 1.821(e). Pursuant to 37 C.F.R. § 1.821(f), or alternatively 37 C.F.R. § 1.825(b), the undersigned states that the copy of the Substitute Sequence Listing in computer readable form is the same as the paper copy of the Substitute Sequence Listing.

Applicant submits that the Sequence List complies with the requirements of 37 C.F.R. §§1.822 and 1.823 and that the application is in condition for allowance, which action is earnestly solcited.

Claim Objections and Rejections Under 35 U.S.C. § 112

The Examiner has objected to an inadvertent typographical error in Claim 57. A period has been inserted at the end of the claim as suggested by the Examiner.

The Examiner has also rejected Claim 23 as allegedly indefinite under 35 U.S.C. § 112, second paragraph. The Examiner has alleged that a concentration comprising about 10^{-21} to about 10^{-14} moles of nucleic acid fragment per 1-10,000 microliters is confusing because it is not clear what the precise concentration is. Applicant submits that amended Claim 23, which recites an amount rather than a concentration of nucleic acid fragment, is definite. Independent Claims 67-68 have been added to further delineate the subject matter to which applicant is entitled. These claims are directed to a method for insertion of a nucleic acid fragment into circular and linear vectors, wherein said method is substantially equally efficient when the

amount of nucleic acid fragment ranges from 10^{-21} to 10^{-14} moles. Support for these claims is present in the specification, for example, at page 21, lines 19-30. Applicant submits that Claims 23, 67 and 68 are definite and requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

The Examiner has also rejected Claims 37, 38, 40, 41, 54, 60 and 61 as allegedly indefinite under 35 U.S.C. § 112, second paragraph. The Examiner has alleged that these claims are indefinite because it is allegedly not clear whether terms "does not substantially" and "are not substantially" indicate that ligase is not present or that it cannot join the cohesive ends. During a telephone interview, Primary Examiner Brusca also indicated that the claim language may be indefinite because that language allegely included the possibility that ligase could be covalently joined to the ends. Applicant submits that amended Claims 37, 40, 54 and 60, which recite that "upon hybridization of said cohesive circularization ends, said cohesive circularization ends cannot be substantially covalently joined by ligase," are definite. Applicant further submits that Claim 61, which recites that "said first nick and said second nick are not substantially covalently joined by ligase," is definite as written. Moreover, the term "substantially" does not render these claims indefinite. *See Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 3 USPQ2d 2010 (Fed. Cir. 1988); MPEP 2173.05(b)D. Accordingly, Applicant respecfully requests withdrawal of this rejection of Claims 37, 38, 40, 41, 54, 60 and 61 as allegedly indefinite under 35 U.S.C. § 112, second paragraph.

Applicant submits that Claims 37, 38, 40, 41, 54, 60 and 61 are product claims directed to vectors, vector-insert constructs, kits, and libraries with particular structural attributes, for example, gaps and 5'-hydroxyls, that substantially limit or eliminate covalent joining by ligase. Applicant submits that these product claims, as written, do not require that ligase be present,

but do describe what would happen if ligase were present -- if ligase were present with these vectors, kits and libraries, no substantial joining of gapped or dephosphorylated cohesive circularization ends would occur. Applicant submits that Claims 37, 38, 40, 41, 54, 60 and 61 are definite and requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Claim Rejections Under 35 U.S.C. § 102

Claims 63-64 have been rejected under 35 U.S.C. § 102(e) as alleged anticipated by Shizuya, 89 Proc. Acad,. Sci.8794-97 (Sept. 1992). According to the Examiner, Shizuya teaches a cDNA library with a size distribution of inserts ranging from 10 to 215 kb and that sampling of the restriction fragment sizes before and that after five days of culture allegedly shows that the library has no substantial size bias.

Claims 63-64 are drawn to genomic or cDNA libraries in linear or circular vectors, wherein said genomic or cDNA library has substantially no insert size bias relative to a population of genomic DNA or cDNA molecules used in making said library.

Applicant submits that while Shizuya may teach that the sizes of various inserts do not change upon culturing through many generations, Shizuya provides no teaching whatsoever on whether or not size bias occurs during insertion of the fragments into vector. Shizuya cloning procedures are essentially standard plasmid cloning procedures (see the section entitled "Cloning Human DNA into pBAC" at pages 8794-8795) with the same size bias problems existing in standard plasmid cloning procedures. Evidence of such size bias exists in Shizuya's statement that "The size distribution of the inserts in Fig. 2A ranges from 10 to 215 kb, with an average size of 100 kb" (page 8795, section "Analysis of the Human Inserts"), whereas the size of the source DNA ranged from 100 to 300 kb (page 8794, section "Cloning Human DNA into pBAC"). Similarly, in the section "Cloning Human DNA in the BAC

Vector" on page 8795 Shizuya states: "As one expects, transformation becomes increasingly more difficult as the size of DNA molecules increases (unpublished observation)... The frequency of transformation with F' lac DNA is about 1/40th that found with pBAC plasmid with no insert." Hence, Shizuya actually would discourage one of skill in the art from seeking the present invention because Shizuya teaches that his DNA libraries did have size bias. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 102(b).

Conclusion

It is believed that the present application is in a condition for allowance which action is earnestly solicited. The Examiner is invited to call the undersigned at (202) 220-4288 to discuss any information concerning this application.

The Office is hereby authorized to charge any fees under 37 C.F.R. § 1.16 or § 1.17 or credit any overpayment to Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON

Date: Feb. 28, 2001

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